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14. ABSTRACT Despite considerable research on health issues affecting the nearly 700,000 U.S. veterans of the 1991 Persian Gulf War, fundamental questions and challenges remain. There is still no widely-accepted case definition for Gulf War illness (GWI) and little current information related to its characteristics. Nor has there been a comprehensive assessment of rates of more familiar diagnosed medical conditions. Gulf War veterans—many still looking for answers about unexplained health problems—have been anxious to participate in studies, while researchers commonly report enormous difficulty identifying adequate numbers of Gulf War veterans for their studies. This project addresses these challenges with a coordinated research effort. Investigators at Baylor University are using a multifaceted survey research strategy to obtain current information on symptoms and medical conditions from a nationally representative sample of 5,000 1991 Gulf War era veterans. These data will be used to optimize a GWI case definition, based on current symptoms, and to provide insights concerning rates of other medical conditions in Gulf War veterans. Parallel to this effort, the project is inviting a broad national sample of Gulf War era veterans to complete health questionnaires by mail or online, and to participate in the 1991 Veterans Research and Information Network (91VetNet), a national research and information resource for Gulf War era veterans and for investigators.					
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**Establishing a 1991 Veterans Research Network  
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## **Introduction**

Despite considerable research on health issues affecting U.S. veterans of the 1990-1991 Persian Gulf War, fundamental questions remain about the health consequences of military service in that conflict. The hallmark health problem associated with 1991 Gulf War military service has been Gulf War illness (GWI), the complex of undiagnosed symptoms that have persisted, for many veterans, for over 20 years. Studies indicate that at least one in four veterans are affected by a generally consistent pattern of excess symptoms, variously defined, that is not attributable to established medical or psychiatric diagnoses, and not explained by clinical diagnostic tests.<sup>1-4</sup> This problem has long been the focus of scientific studies, Congressional inquiries, media reports, and scientific panels.

**The need for current population health data to support an evidence-based Gulf War illness case definition.** The GWI symptom profile typically includes some combination of cognitive difficulties, widespread pain, and unexplained fatigue—accompanied, in many veterans, by chronic digestive problems, respiratory difficulties, and skin abnormalities. Because there are no objective tests that can be used to diagnose GWI, it is currently identified only on the basis of veterans' symptoms. More than 20 years after Desert Storm, however, there is still no widely-accepted case definition for GWI. The 2008 report of the federal Research Advisory Committee on Gulf War Veterans' Illnesses describes eight different approaches used by different investigators to define or characterize GWI.<sup>1</sup> Some case definitions have characterized GWI either very broadly,<sup>5-7</sup> or very narrowly,<sup>8-9</sup> and most were not developed in a systematic, data-driven manner. Despite hundreds of research studies conducted in this population, the lack of a consistent, evidence-based GWI case definition has made study results difficult to interpret and compare and has slowed progress in addressing this problem. Further, there is little available information related to current characteristics of GWI or its impact on the lives of Gulf War veterans.<sup>10</sup>

**The need for systematic, population-based data on other medical conditions affecting 1990-1991 Gulf War era veterans.** Although GWI has been the most prominent health concern associated with the 1991 Gulf War, it is not the only condition of importance. More than 20 years after the war, however, there have been no published studies that provide systematic assessments, in nationally representative samples, of rates at which more familiar diagnosed medical conditions affect 1991 Gulf War veterans.<sup>10</sup> Several studies have reported that 1991 Gulf War veterans have an excess rate of amyotrophic lateral sclerosis (ALS),<sup>11-13</sup> compared to nondeployed veterans of the same era, and one study has provided an indication that 1991 Gulf War veterans suffer from an elevated rate of lung cancer.<sup>14</sup> Mortality studies have also reported that the subgroup of Gulf War veterans potentially exposed to nerve agents in connection with the 1991 Khamisiyah demolitions have died from brain cancers at twice the rate of unexposed veterans.<sup>15,16</sup>

Overall, however, rates of most medical conditions have never been ascertained in 1991 Gulf War veterans. This includes multiple sclerosis, for which a great deal of concern has been raised by Congressional committees, and by veterans' advocates. Data on rates of medical diagnoses in this population are urgently needed, and not only for the insights this information can provide for

veterans and their healthcare providers. In a very practical sense, federal agencies and scientific review panels rely on studies of this type to establish healthcare policies and programs and to determine if veterans should receive disability compensation for diseases that may be related to their military service. Due to the lack of systematic research on diagnosed medical conditions in Gulf War veterans, data are not available to inform veterans, healthcare providers, and policymakers whether U.S. Gulf War veterans are affected by excess rates of most medical conditions of possible concern.

**The need for an information resource for 1990-1991 Gulf War veterans and a mechanism to assist investigators in recruiting Gulf War-era veterans for research studies.** Scientists conducting research on health issues associated with service in the 1990-1991 Gulf War often face serious challenges in carrying out quality research in an effective and efficient manner. This includes an unfortunate dichotomy with respect to recruitment of 1991 Gulf War era veterans for research studies. On one hand, nearly all investigators report enormous difficulty identifying adequate numbers of symptomatic and healthy Gulf War veterans for studies investigating laboratory markers, treatments, and other clinical parameters. As a result, investigators often have no choice but to enroll nearly all veterans they can identify through any means, yielding less-than-ideal study samples that may not be representative of ill veterans more generally. On the other hand, veterans and researchers commonly indicate that Gulf War veterans *want* to participate in studies. Unfortunately, though, there is no unified national veterans group or central contact point that can provide 1991 Gulf War era veterans with information relevant to research or other issues relevant to military service of this period. Veterans of this era, many still seeking answers about unexplained health conditions, are willing and even anxious to participate in research studies, but generally do not know that such studies are being conducted or that they are eligible to participate.

**Project Overview.** Investigators at Baylor University have designed the current project to address these prominent issues with a coordinated effort that utilizes a multipart, national sampling and state-of-the-art survey research strategy. This includes a Computer-Assisted Telephone Interview (CATI) survey of a nationally representative sample of 5,000 1991 Gulf War era veterans, under a contract arrangement with Westat. The CATI survey is designed to provide current data on symptoms and diagnosed medical conditions reported by 3,000 1991 Gulf War veterans, and 2,000 veterans of the same era who did not deploy to the Gulf War theater. In broad consultation with experts in the field, these data will be used to optimize a GWI case definition, based on veterans' current health status, and to provide important insights concerning rates of diagnosed medical conditions in Gulf War era veterans.

The project is also obtaining health data from a second, larger sample, referred to as the network sample. This involves contacting 45,000 Gulf War era veterans to invite them to complete health questionnaires by mail or online. These data will be used to further evaluate patterns observed in the CATI sample, including associations between health outcomes and deployment experiences. In addition, veterans in both the CATI and network samples are invited to participate in the 1991 Veterans Research and Information Network (91VetNet). Participating veterans will receive current information on health issues relevant to military service during 1990-1991 and will be notified about studies for which they may be eligible. The network will also serve as a resource

for scientists conducting research on the health of 1991-era veterans that can assist them in recruiting veterans who may be interested in participating in studies.

Overall, the project is designed to provide current, nationally representative data to identify the prevalence and characteristics of GWI, as well as rates of diagnosed diseases reported by 1991-era veterans. These data will be used to inform veterans, providers, and policymakers, and will also be used to optimize an evidence-based case definition of GWI. In addition, the project will provide a current information resource for 1991-era veterans and a recruitment resource for investigators conducting studies in this population. This is expected to have a positive impact on the broader Gulf War research effort, improving studies to advance GWI treatments and diagnostic tests, and provide insights into its pathobiology.

## **Body**

### **Task 1. Prepare and Submit Documents to Obtain Regulatory Approvals**

This project requires review and approval by two Institutional Review Boards (IRBs) and by the USAMRMC's Office of Human Research Protections (HRPO). In addition, we initially understood, based on information provided by DOD officials, that this project would require review and approval by the federal Office of Management and Budget (OMB), under the federal Paperwork Reduction Act (PRA). We were informed that the OMB approval process typically requires a minimum of eight months. We therefore designed the project timeline to allow ten months for obtaining regulatory approvals, as indicated in the Statement of Work.

Our initial strategy was to begin the process and document submissions required for OMB review and approval prior to HRPO and IRB submissions. This was because we understood that OMB approval would be needed to obtain our initial sampling data from the Defense Manpower Data Center (DMDC), and because the OMB approval process typically takes longer than the IRB process. However, in a concurrent study, we were experiencing extended delays and considerable difficulties in connection with the DOD offices responsible for reviewing and forwarding our PRA documentation to OMB. As of November 2012, these delays had extended the timeline anticipated for OMB review to a minimum of 15 months. We ultimately learned, after multiple requests, contacts, and discussions, that the DOD Information Management Office would consider our previous study to *not* be subject to the federal PRA and that OMB approval would not be required.

For the present study, therefore, before undertaking the lengthy OMB review process, we decided to petition DOD's Information Management Office to obtain a firm decision as to whether the current project falls under the PRA and would be subject to OMB review and approval. Again, after multiple requests, submissions, and discussions over many months, we obtained a ruling from officials at both the DOD Information Management Office and the OMB indicating that the current project would *not* require OMB approval. Email confirmation was received on June 12, 2013. Although obtaining this ruling required an extended effort, it was helpful in allowing our project to proceed without the additional delays inherent in the even lengthier process of OMB review and approval.

We also had initially expected to submit documents on the use of human subjects for Army HRPO review prior to obtaining approvals from Baylor and Westat IRBs, as detailed in the Statement of Work timeline. After the award was made, however, our discussions with HRPO staff indicated that they would prefer to review our submission after IRB approvals were obtained. We are therefore obtaining human subjects' approvals first from Baylor IRB, then from Westat's IRB. On September 3, 2013, we obtained Baylor IRB approval for the national telephone survey, including the study protocol and instrument. We are currently finalizing details with our Westat contractors for submission of all required documents to Westat's IRB. Once Westat IRB approvals are obtained, we will submit required human subjects' documents for the national telephone survey to HRPO for review and approval. We are currently also preparing

documentation, instruments, and design elements required for the online and mail surveys, which are distinct from the CATI survey protocol/documents and do not require review by Westat's IRB.

Our original timeline anticipated that regulatory approvals could be obtained 10 months into the initial project year. While the delays described have resulted in our being several months behind this schedule, we anticipate that the required IRB and HRPO approvals will be obtained in a timely manner, allowing us to move forward with data collection for both surveys in early 2014. This is within the general framework anticipated under the project timeline, which scheduled CATI interviews to begin in month 17 of the project (January 2014) and mail and online survey mailings to be initiated during project months 16 – 20.

## **Task 2. Obtain current data on the health status of 5,000 1991 Gulf War era veterans from a national, representative sample using a Computer Assisted Telephone Interview (CATI) Survey**

We have done considerable preparation at Baylor, and with our contractors at Westat, to work out details of study execution in order to begin CATI interviews early in 2014. This includes working out details of survey instrument design, hiring the epidemiology/survey research postdoctoral fellow who will be working with Dr. Steele on the project, and working out details related to programming CATI questions and skip patterns at Westat. However, we have not yet submitted our DMDC data request for information on 1990-1991 Gulf War era veterans to be included in our sample, since DMDC cannot provide those data until HRPO approvals are obtained.

Because of the extended time allowed in our initial timeline to obtain OMB approvals for this study, it has always been expected that data collection would not begin until the second year of the project.

## **Tasks 3 – 5.**

No activities completed or underway at this time. No subject recruitment or data collection activities have been initiated and no research results are yet available.



## **Key Research Accomplishments**

Only regulatory submissions and work on finalizing study design and instruments has been accomplished to date. Data collection has not yet been initiated.

## **Reportable Outcomes**

There are no manuscripts or other reportable outcomes at this time.

## **Conclusion**

No research results are yet available; no conclusions can be drawn at this time.

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